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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,823	08/16/2006	Toshihiro Nakajima	L7350.0005	6763
32172 7590 10/16/2007 DICKSTEIN SHAPIRO LLP 1177 AVENUE OF THE AMERICAS (6TH AVENUE) NEW YORK, NY 10036-2714			EXAMINER SHIN, DANA H	
			ART UNIT 1635	PAPER NUMBER
			MAIL DATE 10/16/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/568,823	<b>Applicant(s)</b> NAKAJIMA ET AL.	
	<b>Examiner</b> Dana Shin	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 21 February 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 February 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>1-3-07</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of Claims***

Claims 1-18 are currently pending and under examination on the merits.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (*Wands*, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of

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one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims are specifically directed to therapeutic agents comprising siRNA against the gene that codes for Synoviolin for treatment of autoimmune diseases. As such, the claims therapeutic agents must be enabled for therapeutic use in a patient *in vivo* for treating autoimmune diseases at the time the application was filed.

This application claims a foreign priority to a Japanese document 2003-297742, filed on August 21, 2003. Provided that the priority to this document is granted and that the instant specification correctly reflects the original disclosure of the document 2003-297742, the instantly claimed therapeutic agents must have been enabled for therapeutic application in a patient for treatment of autoimmune diseases as of August 21, 2003. However, it is found that the instant specification provides no enabling working example wherein agents comprising a substance that induces ER stress (e.g., tunicamycin) in combination with an siRNA targeted to Synoviolin mRNA indeed treat autoimmune diseases in a living organism. All the working examples in the specification are directed to *in vitro* reduction of Synoviolin expression by an siRNA targeted to Synoviolin in cultured cells *in vitro*. Nowhere in the specification is there a single piece of evidence that the claimed agents are capable of being used in a living organism with a resultant therapeutic effect for autoimmune diseases.

The art-recognized lack of *in vitro-in vivo* correlation of siRNA-mediated gene inhibition due to difficulty of delivering siRNAs into the target cell/tissue in a living organism at the time the invention further requires an *in vivo* working example commensurate in scope with the claims. See for example a post-filing review article by Scherer et al. (*Nature Biotechnology*,

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2003, 21:1457-1465), who teach "The efficiency of delivery will continue to be the limiting factor for stabilized antisense compounds. Delivery is a key concern if the antisense agents are going to be used in a therapeutic setting. To date, there is no single reagent or backbone modification that can be effectively used for all the different antisense agents." See page 1463. They further teach that siRNAs cause off-target effects and induce interferon responses and therefore, using siRNAs as therapeutic agents is still premature. See page 1463.

In light of the above, the *in vitro* examples shown in the specification are not sufficient guidance for making therapeutic agents for treatment of autoimmune diseases, and therefore, one of ordinary skill in the art would not have made the claimed therapeutic agents without performing undue experimentation at the time the invention was made. Accordingly, the invention claimed in claims 7 and 17-18 are rejected as failing to satisfy the enablement requirement set forth in 35 U.S.C. §112, first paragraph.

Claims 11-12 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cell proliferation *in vitro* comprising introducing an siRNA agent targeted to Synoviolin, does not reasonably provide enablement for a method of inhibiting cell proliferation *in vivo* comprising introducing an siRNA agent targeted to Synoviolin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims embrace both *in vitro* and *in vivo* methods comprising introducing siRNA agents.

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The eight factors to be considered for determining whether the specification provides sufficient disclosure to the extent that no undue experimentation would have been necessary as of the earliest filing date sought in the instant application (the year of 2003) are described above.

As stated above, the instant specification provides no enabling *in vivo* working example that shows an siRNA targeted to Synoviolin reduces the Synoviolin mRNA expression, thereby inhibiting cell proliferation in a living organism *in vivo*.

In view of the totality of the eight factors and the reasons stated above, it is concluded that the claimed methods are enabled only insofar as *in vitro* methods.

Claims 1, 3-4, 6-9, 15-16, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

In the instant case, the breadth of claims 1, 3-4, 6-9, 15-16, and 18 embraces both disclosed and yet to be discovered genera of agents and substances that induce apoptosis and ER stress. Although the instant specification discloses several agents and substances that meet the functional requirements set forth in the claims, those agents and substances disclosed therein are

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not a representative number of species for the genera claimed in claims 1, 3-4, 6-9, 15-16, and 18.

Note that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.” See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)(“[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.”). See also MPEP §2163.

In light of the above, the instant specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented the genera claimed in the instant case. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*.” (see page 1117).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 8, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Kaneko et al. (*FEBS Letters*, 2002, 532:147-152, also applicant's citation).

The claims are drawn to an apoptosis-inducing agent that induces ER stress, wherein the agent is tunicamycin or thapsigargin and methods of inhibiting cell proliferation by introducing the apoptosis-inducing agent in cells *in vitro*.

Kaneko et al. teach that thapsigargin and tunicamycin promote ER stress-induced apoptosis in cells, thereby inhibiting cell proliferation *in vitro*. See page 151 and Figure 4. Accordingly, all claim limitations are taught by Kaneko et al.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 8, 10-11, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneko et al. (*FEBS Letters*, 2002, 532:147-152, also applicant's citation) in view of Opalinska et al. (*Nature Reviews Drug Discovery*, 2002, 1:503-514).

Claims are drawn to an apoptosis-inducing agent comprising tunicamycin or thapsigargin and further comprising an siRNA against Synoviolin and a method for inhibiting cell proliferation *in vitro* with the agent further comprising the siRNA.

Applicant's attention is directed to the fact that the claimed Synoviolin is synonymous with HRD1.

Kaneko et al. teach that HRD1 mRNA expression is upregulated in cells in response to ER stresses and that exogenous overexpression of HRD1 gene in cells suppresses ER stress-induced apoptosis (pages 150-151). They also teach that thapsigargin and tunicamycin promote ER stress-induced apoptosis in cells, thereby inhibiting cell proliferation *in vitro*. Kaneko et al. do not teach siRNA against HRD1 mRNA (or synoviolin), nor do they teach combining the thapsigargin with siRNA agent for inhibiting cell proliferation.

Opalinska et al. teach that siRNAs, similar to antisense oligonucleotides and ribozymes, inhibit target mRNA expression in cells *in vitro* (page 505).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an siRNA molecule against the HRD1 mRNA sequence of Kaneko et al. and combine it with either thapsigargin or tunicamycin in order to induce cell apoptosis, thereby inhibiting cell proliferation *in vitro*.

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One of ordinary skill in the art would have been motivated to do so because siRNA molecules were known to inhibit target mRNA expression as taught by Opalinska et al., and because the instantly claimed target mRNA sequence of Synoviolin (or HRD1) was taught by Kaneko et al. Since the technique and skill to make an siRNA molecule were available in the art at the time of the invention, the skilled artisan would have had a reasonable expectation of success in making an siRNA molecule against the claimed Synoviolin gene sequence. Furthermore, since Synoviolin was known to suppress ER stress-induced apoptosis in cells *in vitro*, it would have been obvious to one of ordinary skill in the art that inhibiting Synoviolin expression in cells by means of siRNA would induce cellular apoptosis and doing so would inhibit cellular proliferation. Further, the skilled artisan would have been motivated to combine the known apoptosis inducing drugs, thapsigargin and tunicamycin, with an anti-Synoviolin siRNA molecule because both function as apoptosis inducer or cell proliferation inhibitor, and therefore, it would have seemed logical to the skilled artisan to combine the two agents for an additive or synergistic effect of inhibiting cellular proliferation in cells *in vitro*.

See also *In re Kerkhoven*, wherein the court expressed the following:

“It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Since both Synoviolin mRNA expression inhibitor and thapsigargin/tunicamycin were recognized in the art as anti-proliferative or pro-apoptotic agents, it would have been *prima facie*

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obvious to combine them for enhanced cell proliferation inhibition with a reasonable expectation of success. See also MPEP 2144.06.

Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-6, 8-9, and 13-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9, and 14 of copending Application No. 11/631,283. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims sets are drawn to inhibitors/therapeutic agents/methods for inhibiting Synoviolin.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8-18, and 21-25 of copending Application No. 10/592,918. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims sets are drawn to inhibitors/therapeutic agents/siRNA agents/methods for inhibiting Synoviolin, thereby treating autoimmune diseases.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin  
Examiner  
Art Unit 1635

/J. E. Angell/  
Primary Examiner  
Art Unit 1635